REMARKS

Claims 19- 36 are currently pending in the present application.

For clarity, without prejudice or disclaimer, claims 1, 5, 6, 10, 11, 13 and 15 -18 have been cancelled and new claims 19-34 have been added. The new claims, corresponding cancelled claims, and at least some additional support from the original specification are summarized in Table 1.

Table 1

New Claims	**Corresponding Original Claims**	**Some Additional Support in Original Specification**
19	1	Example 2, page 9, line 8 – page 13, line 19, page 27, lines 1-23
20, 22	11	
21, 23	5 and 6, respectively	
24	12	Sequence listed in SEQ ID NO:15
25	10	page 2, lines 5-9
26	none	page 27, lines 4 and 5
27	16	
28	13	Example 2, page 12, line 22 – page 13, line 19
29	none	page 13, line 20 – page 14, line 12
30	none	Example 3, page 14, line 13 – page 15, line 9
31	none	page 15, line 10 – page 16, line 24
32-34	none	Example 4, page 9, lines 6 and 7
35-36	none	page 18, line 2 – page 19, line 9

As summarized in Table 1, it is respectfully submitted that the amendments made herein are supported by the specification and the original claims and introduce no new subject matter. Additionally, no additional claim fees are necessitated. Moreover, it is believed that the new claims overcome the Examiner's rejections and objections as discussed below. Entry of the amendments made herein is proper and respectfully requested.

Applicants are pleased to note that all of the prior rejections under 35 U.S.C. § 101, 102 and 112, for lack of enablement and for double patenting, have been withdrawn.

Claim Objections

Applicants respectfully submit that as with any polypeptide, "a" should be used to modify "B-domain deleted human clotting factor VIII (FVIII) polypeptide" when the polypeptide is first mentioned in a claim. Therefore, it is proper for new claim 19 to recite "a", instead of "the", in front of "B-domain deleted human clotting factor VIII (FVIII) polypeptide".

All new claims are limited to a non-human transgenic mammal as suggested by the Examiner.

New claim 25, corresponding to the canceled claim 10, has clearly set out that "the B-domain deleted human FVIII polypeptide is proteolytically processed intracellularly into a light chain having the A3, C1 and C2 domains and a heavy chain having the A1 and A2 domains, wherein the light chain and heavy chain are operably linked by a junction." Support for the clarification can be found at least from page 2, lines 5-9, of the original specification.

In view of the above amendments, withdrawal of claim objections are respectfully requested.

Claim Rejections for Indefiniteness

Claim 19 clearly recites that the B-domain deleted human FVIII polypeptide lacks its innate signal peptide. As known to a person skilled in the art, a signal sequence is required for the secretion of a protein. An "innate" signal sequence refers to the naturally occurring signal sequence for a secreted protein. In this case, the innate signal sequence for the B-domain deleted human FVIII polypeptide has been removed and replaced with a mammary gland-specific signal peptide. Claim 24 clearly recites that SEQ ID NO:15 is the recombinant polypeptide that comprises the signal peptide of bovine α-S1 casein peptide of SEQ ID NO:14 and the B-domain deleted human FVIII polypeptide lacking its innate signal peptide. Support for claim 24 is found at least from the actual sequence listed in SEQ ID NO:15.

In view of the amendments, it is believed that all of the indefiniteness rejections under 35 U.S.C. § 112, second paragraph have been overcome. Reconsideration and withdrawal of these rejections are respectfully requested.

Claim Rejections for Obviousness

The Examiner has rejected various claims under 35 U.S.C. §103(a) as being unpatentable over the combination of various prior art references.

Reconsideration and withdrawal of the rejection and allowance of the pending claims are respectfully requested for at least the following reasons.

After entry of the current claim amendments, claim 19 is the only independent claim. Claim 19 recites, *inter alia:*

"A non-human transgenic mammal selected from the group consisting of mice, rats, goats, pigs, sheep and cows, whose genome comprises:

(a) an α-lactalbumin (α-LA) promoter; and

(b) a nucleotide sequence linked to the α-LA promoter, the nucleotide sequence encoding a recombinant polypeptide comprising a mammary gland-specific signal peptide and a B-domain deleted human clotting factor VIII (FVIII) polypeptide lacking its innate signal peptide..."

The cited prior art references, Chen, *Transgenic Research*, 11:257-268, 2002 (Chen"), Soukharev, *Blood Cells, Molecules and Diseases*, 28:234-248, 2002 ("Soukharev"), Lubon U.S. Patent 6,255,554 ("Lubon"), and DeBoer U.S. Patent 5,633,076 ("DeBoer"), taken alone or in combination, fail to disclose or suggest a non-human transgenic mammal having an α-lactalbumin (α-LA) promoter linked to a nucleotide sequence encoding a recombinant polypeptide comprising a mammary gland-specific signal peptide and a B-domain deleted human clotting factor VIII (FVIII) polypeptide ("BDD-rFVIII").

The Examiner has the burden of establishing a *prima facie* case of obviousness. M.P.E.P. §2142. The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or that knowledge generally available to one of ordinary skill in the art would lead the

individual to combine the relevant teachings of the references in the manner suggested by the Examiner. M.P.E.P. §2143.01.

The Examiner acknowledges that Chen does not disclose a BDD-rFVIII. Applicants respectfully submit that Soukharev fails to compensate for the deficiencies of Chen. Although Soukharev suggests that the removal of the B domain may improve the yield of FVIII, Soukharev does not teach how to make a transgenic animal that secrets the BDD-rFVIII in milk. Indeed, Soukharev recites:

> Theoretically, the use of BDD-rFVIII might further increase the yield of FVIII secreted into milk, but there is no information whether transgenic animals of this type have been developed. Page 241, col. 2, lines 1-5. (Emphasis Added)

Given the unpredictability of the transgenic animal art, based on the objective teaching of Chen and Soukharev, without undue experimentation, one of ordinary skill in the art would not have known whether a transgenic mammal that secrets BDD-rFVIII in milk, as claimed in instant claim 19, could ever be made. It is well known to a person skilled in the art that *in vitro* results can not always be reproduced *in vivo*, see DECLARATION OF Dr. CHUAN-MU CHEN UNDER 37 C.F.R. § 1.132 ("Declaration"). Indeed, without actually making and analyzing the claimed transgenic mammal, one would not have known whether it is practicable at all to made such a transgenic mammal. For example, one would not know whether the BDD-rFVIII protein could ever be secreted in a transgenic mammal's milk, whether the protein could be processed and folded properly in the milk, whether the protein could have any biological activity in the milk, whether the protein could be produced at high enough concentration in the milk, etc.

Lubon fails to compensate for the deficiencies of Chen and Soukharev. Lubon's transgenic mammal has a second exogenous gene construct, which includes DNA encoding von Willebrand Factor or fragment thereof. Lubon does not teach or suggest a transgenic animal of the instant claim 19, i.e., one which secrets BDD-rFVIII in milk without the second exogenous gene construct.

DeBoer fails to compensate for the deficiencies of Chen, Soukharev, and Lubon. Nowhere does DeBoer describe or suggest that a BDD-rFVIII protein can be produced in milk of a transgenic animal. DeBoer provides merely a potential use of the mammary gland-specific vector including bovine αS1-Casein promoter and enhancer in the production of human proteins including lactoferrin, immunoglobulin, FVIII, factor IX, protein C, lysozyme and serum protein. A full-length FVIII is genetically different from a BDD-rFVIII protein. DeBoer neither teaches nor suggests the production of a BDD-rFVIII protein with a relatively high yield from a transgenic animal. One skilled in the art would not be motivated to carry out the claimed invention based on the disclosure of DeBoer.

By using the proper promoter (*i.e.*, the α-LA promoter) and by actually constructing and testing the transgenic animals, Applicants discovered for the first time that a transgenic mammal that secrets BDD-rFVIII protein in its milk is not only practicable, but also superior than other transgenic mammals. As stated in the Declaration, the transgenic mammal of the instant claim produced BDD-rFVIII in its milk at more than 50 μg/mL, and the clotting activity of the milk reached a level of 25-fold higher than that of normal human plasma. None of prior art references has taught or suggested such superior results.

While any judgment of obviousness is based on hindsight reasoning, it is only permissible to take into account knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and without including knowledge gleaned *only* from the Applicant's disclosure. M.P.E.P. §2145, X, A. The Examiner appears to have impermissibly relied on the Applicants' disclosure in order to modify the prior art references, because there is no reasonable expectation of success in the prior art as to the combination and/or modification of the prior art references.

For reasons discussed above, Applicants respectfully submit that claim 19 is not *prima facie* obvious under 35 U.S.C. § 103(a) over Chen, Soukharev, Lubon and DeBoer. Claims 20-36 are also not *prima facie* obvious under 35 U.S.C. § 103(a) over Chen, Soukharev, Lubon and DeBoer, because they all, directly or indirectly, depend from claim 19.

Claims 22-24 are further not *prima facie* obvious under 35 U.S.C. § 103(a) over Chen, Soukharev, Lubon and DeBoer, because the references, taken alone or in combination, fail to disclose or suggest a non-human transgenic mammal having an α-lactalbumin (α-LA) promoter linked to a nucleotide sequence encoding a recombinant polypeptide comprising bovine α-S1 casein signal peptide and a BDD-rFVIII.

The Examiner acknowledges that the combination of Chen and Soukharev does not teach using the 15 amino acid bovine α-S1 casein signal peptide. Applicants respectfully submit that DeBoer fails to compensate for the deficiencies of Chen and Soukharev. As discussed above, DeBoer does not provide a reasonable expectation of success as to the production of a transgenic animal that secrets a BDD-rFVIII protein with a relatively high yield in the milk. DeBoer discloses the use of a bovine αS1-CN (16-kb) promoter. In addition to the unknown factors discussed above, it is not even known whether a bovine α-S1 casein signal peptide of DeBoer could have worked properly with the α-LA promoter (2.0 kb) or the BDD-rFVIII of the instant application, without undue experimentation. Again, the Examiner appears to have impermissibly relied on the Applicants' disclosure in order to modify the prior art references.

Applicants therefore respectfully request that the rejections under 35 U.S.C. §103(a) over the prior art references be withdrawn.

CONCLUSION

In view of the foregoing amendment, Applicants respectfully submitted that the present application as claimed in claims 19-36, is in condition of allowance and such action is respectfully requested.

Respectfully submitted,

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Declaration of Chuan-Mu Chen Under 37 C.F.R. § 1.132